



# Clinical Validity of a Normal Pulmonary Angiogram in Patients with Suspected Pulmonary Embolism – A Critical Review

EDWIN J. R. VAN BEEK\*, ELISE M. J. BROUWERS†, BIN SONG‡, PAUL D. STEIN§, MATTHIJS OUDKERK¶

\*Section of Academic Radiology, Royal Hallamshire Hospital, Sheffield, U.K., †Department of Radiology, Ikazia Ziekenhuis, Rotterdam, The Netherlands, ‡The First University Hospital, West China University of Medical Sciences, Chengdu, People's Republic of China, §St Joseph Mercy Oakland Research Office, Pontiac, Michigan, U.S.A. and ¶Department of Radiology, Academic Hospital Groningen, Groningen, The Netherlands

Received: 18 December 2000 Revised: 26 March 2001 Accepted: 10 April 2001

**AIM:** To determine the validity of a normal pulmonary angiogram in the exclusion of pulmonary embolism (PE), based on the safety of withholding anticoagulant therapy in patients with a normal pulmonary angiogram.

**MATERIALS AND METHODS:** A review of English reports published between 1965 and April 1999 was carried out. Eligible articles described prospective studies in patients with suspected PE and a normal pulmonary angiogram, who remained untreated and were followed-up for a minimum of 3 months. Articles were evaluated by two authors, using pre-defined criteria for strength of design. End points consisted of fatal and non-fatal recurrent thromboembolic events. A sensitivity analysis was performed, by removing one study at a time from the overall results and by comparing pre- and post-1990 publications.

**RESULTS:** Among 1050 patients in eight articles included in the analysis, recurrent thromboembolic events were described in 18 patients (1.7% 95% CI: 1.0–2.7%). These were fatal in three patients (0.3% 95% CI: 0.02–0.7%). The recurrence rate of PE decreased from 2.9% (95% CI: 1.4–6.8%) before 1990 to 1.1% (95% CI: 0.5–2.2%) after 1990.

**CONCLUSION:** It would appear that the ability to exclude PE by angiography has improved over the years, as indicated by recurrence rate of PE. The low recurrence rate of PE supports the validity of a normal pulmonary angiogram for the exclusion of PE. van Beek, E. J. R. *et al.* (2001). *Clinical Radiology* 56, 838–842.

© 2001 The Royal College of Radiologists

**Key words:** diagnosis, pulmonary embolism, pulmonary angiography, review.

Recently, the value of pulmonary angiography in subsegmental (i.e. small) pulmonary emboli (PE) has become an issue of discussion [1]. In this study it was reiterated that subsegmental PE may result in a decrease in interobserver agreement, rendering pulmonary angiography less reliable. The discussion mirrored previous studies, which assessed intra- and interobserver variation in pulmonary angiography [2–4]. It was also suggested that conventional pulmonary angiography may not be a proper reference test in patients with suspected pulmonary embolism and small PE [1,5].

It is difficult to assess the value of a diagnostic test if it is commonly regarded as the reference method. One way of addressing the value of a normal test result is to scrutinize patients who are suspected of the disease, but who remain

untreated as a result of a normal test result. In patients with suspected pulmonary embolism in whom the diagnosis is missed, this would likely lead to recurrent thromboembolic events [6].

We performed a critical review of studies, which used pulmonary angiography as a final diagnostic test to clarify the clinical validity of a normal pulmonary angiogram in patients with clinically suspected PE.

## MATERIALS AND METHODS

Articles were identified through the Medline database and Current Contents, which described diagnostic management studies in patients with suspected pulmonary embolism. The search was limited to articles published in the English language during the period 1965 to 1 March 1999. Retrospective studies, review articles and abstracts were not included in the analysis. The following search terms were

Author for correspondence and guarantor of study: Dr Edwin J. R. van Beek, Section of Academic Radiology, Royal Hallamshire Hospital, Floor C, Glossop Road, Sheffield S10 2JF, U.K. Fax: +44 114 2724760; E-mail: [e.vanbeek@sheffield.ac.uk](mailto:e.vanbeek@sheffield.ac.uk)

**Table 1 – Management studies in patients with clinically suspected pulmonary embolism in whom anticoagulants were withheld based on a normal pulmonary angiogram**

Authors	Follow-up		Pulmonary embolism (PE)				
	Year	Months	Complete (%)	Fatal (%)	Non-fatal (%)	Any PE	(%95% CI)
Novelline <i>et al.</i> [16]	1978	6	167 (86)	0/167 (0)	3/167 (1.8)	3/167	(1.8; 0.5–6.1)
Cheely <i>et al.</i> [14]	1981	12	144 (94)	0/144 (0)	6/144 (4.2)	6/144	(4.2; 1.5–9.1)
Hull <i>et al.</i> [15]	1988	3	34 (100)	1/34 (2.9)	0/34 (0)	1/34	(2.9; 0.1–15.3)
Henry <i>et al.</i> [18]	1995	12	380 (100)	2/380 (0.5)	4/380 (1)	6/380	(1.5; 0.5–3.4)
Van Rooij <i>et al.</i> [20]	1995	3	129 (95)	0/95 (0)	1/95 (1)	1/95	(1; 0.02–4.2)
Van Beek <i>et al.</i> [21]	1996	6	105 (100)	0/105 (0)	0/105 (0)	0/105	(0; 0–3.5)
Forauer <i>et al.</i> [23]	1998	6	54 (89)	0/54 (0)	0/54 (0)	0/54	(0; 0–6.6)
Perrier <i>et al.</i> [24]	1999	3	37 (100)	0/37 (0)	1/37 (2.7)	1/37	(2.7; 0.1–14.2)
Total			1050 (95)	3/1050 (0.3)	15/1050 (1.4)	18/1050	(1.7; 1–2.7)

used: ‘diagnosis’, ‘pulmonary embolism’, ‘pulmonary angiography’ and ‘follow-up’. The bibliographies of the identified publications were also checked for potentially eligible studies.

From the identified studies, a selection was made of articles, which used pulmonary angiography as the final diagnostic test. Selective cut-film, selective digital subtraction angiography and selective cine-angiography were all accepted techniques. Intravenous digital subtraction angiography was excluded from the analysis. Patients who had a normal pulmonary angiogram in whom therapeutic anticoagulation was withheld were the focus of the analysis. The end points used were fatal and non-fatal thromboembolic events.

Articles were assessed for methodological strength on the basis of six items. For each item that was included in the report, one point was given leading to a maximum score of 6 points. The items scored included: (1) type of publication (peer-reviewed full paper); (2) inclusion and exclusion criteria clearly described; (3) clinical characteristics of study groups adequately described (at least two of the following had to be mentioned: age, sex, clinical suspicion of PE, risk factors, in- or out-patients); (4) technique of pulmonary angiography; (5) description of follow-up (i.e. telephone or clinical visit, duration at least 3 months); (6) description of diagnosis in patients with recurrent symptoms. A study was considered to be of strong methodology if all six items were satisfied and of reasonable strength if five out of six items were satisfied.

An analysis was performed by means of a primary assessment of recurrent (fatal and non-fatal) PE with exclusion of patients lost to follow-up. Overall, 95% confidence intervals were calculated. To test potential influence of individual studies, a sensitivity analysis was performed which involved the removal of each individual study from the results. A second analysis compared the results in studies prior to 1990 with those of studies after 1990. Furthermore, the analysis was extended into a worst case scenario (where all patients lost to follow-up were assumed to have died due to recurrent PE) and a best case scenario (all patients lost to follow-up uneventful).

## RESULTS

A total of 12 studies were identified which assessed the value of pulmonary angiography [14–25]. Four of these studies had to be excluded from the analysis [17,19,22,25]. The main reason for exclusion was a lack of data on follow-up and outcome of patients with a normal pulmonary angiogram [19,22,25]. One report did not give long-term follow-up on some of the patients (those who were not randomized for investigation [17]). Furthermore, one report only gave short-term follow-up data as part of the prospective investigation of pulmonary embolism diagnosis (PIOPED) [26]. Long-term follow-up was subsequently reported among the 380 randomized patients in PIOPED who had negative pulmonary angiograms and did not receive anticoagulants [18]. It was decided to focus on the long-term follow-up study only.

The eight included studies all scored 5 or more points for methodological strength. The results of these studies are summarized in Table 1. The publication dates ranged from 1978 to 1999. Follow-up ranged from 3 months to 1 year. A total of 51 patients were lost to follow-up. Anticoagulant therapy, with therapeutic levels of heparin or oral anticoagulant drugs, was withheld in 1050 patients with a normal pulmonary angiogram. Recurrent PE occurred in 18 patients (1.7%; 95% CI: 1.0–2.7%) and three of these events were fatal (0.3%; 95% CI: 0.02–0.7%).

With the exception of one study where pulmonary angiography was used in the management of only a few patients [24], it becomes clear that the oldest three studies [14–16] tend to have slightly higher recurrence ratios than the studies published after 1990 [18,20,21,23,24]. Comparison of the results of the three oldest studies with the five later studies showed recurrent PE to be more frequent in the older studies: 2.9% (95% CI: 1.4–6.8%) vs 1.1% (95% CI: 0.5–2.2%).

## SENSITIVITY ANALYSIS

Assuming that all patients who were lost to follow-up died from a fatal PE (worst case scenario), recurrent PE

would have occurred in 69 patients (6.3%; 95% CI: 4–7%) with a fatality rate of 4.9% (95% CI: 3–6%). In a best case scenario, where all patients lost to follow-up remained uneventful, the recurrent PE and fatal PE rate would have been 1.6% (95% CI: 1.0–2.6%) and 0.27% (95% CI: 0.02–0.6%), respectively.

The removal of one study with 154 patients [14] resulted in a decrease of recurrent PE from 1.7% to 1.3%. Removal of one of the other studies resulted in a consistent recurrence rate of 1.7–1.9%.

## DISCUSSION

Pulmonary angiography continues to be the reference test in patients with clinically suspected PE and non-diagnostic non-invasive test results. Even so, it has been suggested that the sensitivity of pulmonary angiography for subsegmental emboli is suboptimal and that pulmonary emboli could be missed as a result [12].

How can we evaluate whether a diagnostic test, which is generally considered as reference standard for the exclusion of an illness, is clinically valid? A means of addressing this issue is by observing the outcome of patients who have a normal test result and who therefore remain untreated. Based on previous and limited literature, one could expect a 30% fatal pulmonary embolism rate and a 30% non-fatal embolism rate [13]. Therefore, one would expect a large number of thromboembolic events if the diagnosis of pulmonary embolism were missed and patients would inadvertently remain untreated.

In the current review, we pooled the findings of studies that were of good design, as defined *a priori*. A total of eight studies with 1050 patients with normal pulmonary angiograms were identified. Among these, recurrent non-fatal and fatal pulmonary embolism following normal angiography occurred in 1.4% and 0.3%, respectively. In a hospital setting, patients have co-morbid conditions and high-risk situations for the development of thromboembolism. Thus, patients with negative angiography findings may develop thromboembolic complications at a higher frequency than in the general population. Another issue is that physicians may have a lower threshold of suspicion, resulting in increased number of patients referred for diagnosis and more normal diagnostic findings in the presence of continuing risk factors for the development of venous thromboembolic disease. In spite of this background, the recurrence rates following normal angiography compare favourably with other diagnostic management strategies.

Although pulmonary angiography has become a much safer procedure, there is still great reluctance to apply it in patients with suspected pulmonary embolism. Questionnaires among physicians in The Netherlands and in the U.K. have demonstrated that less than 10% of patients who may require pulmonary angiography actually undergo this test [27,28]. Some of the reasons for this under-use of angiography are probably related to the fear of an invasive diagnostic tests, old perceptions of risk and the difficulty

with which pulmonary angiography is available in a routine clinical setting.

The use of helical computed tomography (CT) has been advocated for the demonstration and exclusion of pulmonary embolism. The availability of helical CT, its non-invasive nature and the relative ease of the procedure certainly render it an extremely useful diagnostic test for the management of suspected PE. Some caution is, however, required before one applies helical CT as a routine clinical procedure. There are only a few prospective management studies in patients with suspected PE who were treated on the basis of helical CT findings [29,30]. One study in which patients remained untreated following a non-diagnostic lung VQ scintigram, normal duplex studies of the leg veins and normal helical CT reported a recurrence rate of 5.5% (95% CI: 2–12%) and a fatal recurrence rate of 1% (95% CI: 0.02–5.4%) [29]. A more recent study directly compared a management strategy based on lung scintigraphy with helical CT [30]. The recurrence rate of patients who remained untreated following normal helical CT (2/198) were virtually equivalent to patients who were followed following a normal perfusion lung scan (0/188). One of the criticisms of this study is the potential for selection bias: in the group with a normal helical CT, 70% remained untreated, 8% were lost to follow-up and 22% received anticoagulant therapy regardless [30].

Two other retrospective studies in patients with suspected PE who were apparently managed on the basis of helical CT findings have been published [31,32]. In one study in 126 patients, follow-up was complete in 78 patients with a normal helical CT result who remained untreated [31]. None died from recurrent PE, while one patient had a small PE confirmed at autopsy which was not thought to have contributed to death. Another review of 143 patients focused on 113 patients with normal helical CT who remained untreated [32]. During follow-up, 13 were lost, 19 died (none reportedly from PE), while no recurrent PE was documented in the remaining 81 patients. A recent meta-analysis came to the conclusion that the safety of withholding anticoagulant therapy in patients with a normal helical CT angiogram requires further confirmation [33].

A final point of interest is the fact that anticoagulant therapy inherently carries the risk of bleeding complications. In this light, it deserves mention that the outcome of patients with normal pulmonary angiography compares favourably with the outcome of patients with proven PE who received anticoagulant therapy [9,10,34,35]. This emphasizes the role that any diagnostic test has to play: the safe exclusion of PE leads to the withholding or withdrawal of anticoagulant therapy and its associated bleeding risks. It would appear that this is the case in patients with suspected pulmonary embolism and normal angiographic findings.

Every literature review has limitations. First, potential selection bias can never be excluded. We used two databases and performed a search of the references in these articles. Nevertheless, publication of articles is often related to a more positive outcome. This problem is impossible to solve, and therefore one should remain cautious of the findings of



a critical review. Second, we did not include published abstracts because these are insufficiently peer-reviewed and may contain inaccuracies. In spite of these limitations, the figures seem relatively robust, as shown by the sensitivity analysis. With the exception of one, older study, no major shift in recurrence rate was observed.

Studies published prior to 1990 showed a trend towards higher recurrent PE rates than the more modern studies. This difference in outcome may, in part, be the result of changing technology and imaging equipment. The introduction of digital subtraction angiography has changed the image analysis since the 1990s. The studies published after 1995 all used this new technology. Digital subtraction angiography decreases inter-observer variability [4–6]. Therefore, it may improve the confidence with which PE is excluded. Another potential explanation may be that the findings may be a reflection of a changing pattern of severity of venous thromboembolism. This could result in a decreased chance of recurrent disease, which may in part be the effect of more widespread use of anticoagulant prophylaxis using low-dose heparin regimens.

The worst case scenario assumes all patients lost to follow-up died from a recurrent PE. Naturally, this is a gross overestimation of what can be expected. It also shows figures, which are in sharp contrast with clinical experience and the evaluated studies. Furthermore, this scenario is heavily weighted by the oldest studies, which account for more than two-thirds of those lost to follow-up. In the absence of the oldest three studies, the overall occurrence in this scenario on follow-up of non-fatal and fatal PE is 3.1% and 2.3%, respectively. These figures approximate those of the earlier described study, which included helical CT for the management of patients with suspected PE [27]. However, the more recent study with helical CT showed better outcome figures [30].

It is unknown whether patients who suffer a PE several weeks or months after a negative pulmonary angiogram had a false-negative angiogram with recurrent PE or a first occurrence of PE. The PIOPED study performed early follow-up in 480 patients with normal angiographic findings. The outcome classification committee reversed the report in four patients, who died within 2–6 days of their negative angiogram and had PE confirmed at autopsy [26]. Many patients with suspected pulmonary embolism have continuing risk factors, such as prolonged immobilization and malignancy, which could result in a (new) thromboembolic event. The risk of recurrence has to be weighed against the risks of (inadequate) anticoagulant therapy. In the present analysis, a normal pulmonary angiogram seems safe enough to indicate withdrawal or withholding of anticoagulant therapy.

We suggest that there is still a role for pulmonary angiography, as a final diagnostic test in the work-up of patients with suspected PE. However, it seems justified to use non-invasive diagnostic tests to their full potential. Several strategies have been suggested that will decrease the number of patients who require angiography [24,36–40]. However, there will still be patients in whom all non-invasive tests are non-diagnostic [24]. The present analysis

strengthens the evidence that pulmonary angiography is able to adequately exclude PE and should be performed as a final diagnostic test. This approach is much safer than the current practice of (long-term) anticoagulant therapy in these patients [38,40,41]. Pulmonary angiography should still be considered the reference method for the exclusion of pulmonary embolism. It is safe to withhold anticoagulant therapy in patients with suspected pulmonary embolism and a normal pulmonary angiogram.

## REFERENCES

- 1 Oser RF, Zuckerman DA, Gutierrez FR, Brink JA. Anatomic distribution of pulmonary emboli at pulmonary angiography: implications for cross-sectional imaging. *Radiology* 1996;199:31–35.
- 2 Diffin DC, Leyendecker JR, Johnson SP, Zucker RJ, Grebe PJ. Effect of anatomic distribution of pulmonary emboli on inter-observer agreement in the interpretation of pulmonary angiography. *AJR* 1998;171:1085–1089.
- 3 Stein PD, Henry JW. Prevalence of acute pulmonary embolism in central and subsegmental pulmonary arteries and relation to probability interpretation of ventilation/perfusion lung scans. *Chest* 1997;111:1246–1248.
- 4 Van Beek EJR, Bakker AJ, Reekers JA. Interobserver variability of pulmonary angiography in patients with non-diagnostic lung scan results: conventional versus digital subtraction arteriography. *Radiology* 1996;198:721–724.
- 5 Johnson MS, Stine SB, Shah H, Harris VJ, Ambrosius WT, Trerotola SO. Possible pulmonary embolus: evaluation with digital subtraction versus cut-film angiography – prospective study in 80 patients. *Radiology* 1998;207:131–138.
- 6 Hagspiel KD, Polak JF, Grassi CJ, Faitelson BB, Kandarpa K, Meyerovitz MF. Pulmonary embolism: comparison of cut-film and digital pulmonary angiography. *Radiology* 1998;207:139–145.
- 7 Remy-Jardin M, Remy J, Deschildre F, et al. Diagnosis of pulmonary embolism with spiral CT: comparison with pulmonary angiography and scintigraphy. *Radiology* 1996;200:699–706.
- 8 Van Rossum AB, Pattynama PMT, Tjin A Ton ER, et al. Pulmonary embolism: validation of spiral CT angiography in 149 patients. *Radiology* 1996;201:467–470.
- 9 Van Beek EJR, Kuyper PMM, Büller HR, Brandjes DPM, Bossuyt PMM, ten Cate JW. The clinical course of patients with suspected pulmonary embolism. *Arch Intern Med* 1997;157:2593–2598.
- 10 Douketis JD, Kearon C, Bates S, Duku EK, Ginsberg JS. Risk of fatal pulmonary embolism. *JAMA* 1998;279:458–462.
- 11 Stein PD, Henry JW, Relyea B. Untreated patients with pulmonary embolism. Outcome, clinical and laboratory assessment. *Chest* 1995;107:931–935.
- 12 Stein PD, Henry JW, Gottschalk A. Reassessment of pulmonary angiography for the diagnosis of pulmonary embolism: relation of interpreter agreement to the order of the involved pulmonary arterial branch. *Radiology* 1999;210:689–691.
- 13 Barrit DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism. A controlled study. *Lancet* 1960;i:1309–1312.
- 14 Cheely R, McCartney WH, Perry JR, et al. The role of noninvasive tests versus pulmonary angiography in the diagnosis of pulmonary embolism. *Am J Med* 1981;70:17–22.
- 15 Hull RD, Raskob GE, Carter CJ, et al. Pulmonary embolism in outpatients with pleuritic chest pain. *Arch Intern Med* 1988;148:838–844.
- 16 Novelline RA, Baltarowich OH, Athanasoulis CA, et al. The clinical course of patients with suspected pulmonary embolism and a negative pulmonary arteriogram. *Radiology* 1978;126:561–567.
- 17 Stein PD, Athanasoulis C, Alavi A, et al. Complications and validity of pulmonary angiography in acute pulmonary embolism. *Circulation* 1992;85:462–468.
- 18 Henry JW, Relyea B, Stein PD. Continuing risk of thromboemboli among patients with normal pulmonary angiograms. *Chest* 1995;107:1375–1378.

- 19 Hedlund B, Lassvik C, Nilsson S, Ohlsson J, Stomeus S. A prospective, comparative study of ventilation-perfusion scintigraphy and clinical evaluation versus digital subtraction angiography in acute pulmonary thromboembolism. *Eur Radiol* 1995;5:427-434.
- 20 Van Rooy WJJ, den Heeten GJ, Sluzewski M. Pulmonary embolism: diagnosis in 211 patients with use of selective pulmonary digital subtraction angiography with a flow-directed catheter. *Radiology* 1995;195:793-797.
- 21 Van Beek EJR, Reekers JA, Batchelor D, Brandjes DPM, Peeters FLM, Büller HR. Feasibility, safety and clinical utility of angiography in patients with suspected pulmonary embolism and non-diagnostic lung scan findings. *Eur Radiol* 1996;6:415-419.
- 22 Jacobson AF, Patel N, Lewis DH. Clinical outcome of patients with intermediate probability lung scans during six-month follow-up. *J Nucl Med* 1997;38:1593-1596.
- 23 Forauer AR, McLean GK, Wallace LP. Clinical follow-up of patients after a negative digital subtraction pulmonary arteriogram in the evaluation of pulmonary embolism. *JVIR* 1998;9:903-908.
- 24 Perrier A, Desmarais S, Miron MJ, *et al.* Non-invasive diagnosis of venous thromboembolism in outpatients. *Lancet* 1999;353:190-19.
- 25 Nilsson T, Turen J, Billstrom A, Mare K, Carlsson A, Nyman U. Validity of pulmonary cine arteriography for the diagnosis of pulmonary embolism. *Eur Radiol* 1999;9:276-280.
- 26 The PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism: results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). *JAMA* 1990;263:2753-2759.
- 27 Kuijter PMM, Turkstra F, van Beek EJR, ten Cate JW, Büller HR. A survey of the diagnostic and therapeutic management of patients with suspected pulmonary embolism in The Netherlands. *Neth J Med* 1997;50:261-266.
- 28 Burrill GJ, Bell JR, Padley SP. Survey on the use of pulmonary scintigraphy, spiral CT and conventional pulmonary angiography for suspected pulmonary embolism in the British Isles. *Clin Radiol* 1999;54:807-810.
- 29 Ferretti GR, Bosson JL, Buffaz PD, *et al.* Acute pulmonary embolism: role of helical CT in 164 patients with intermediate probability at ventilation-perfusion scintigraphy and normal results at duplex US of the legs. *Radiology* 1997;205:453-458.
- 30 Goodman LR, Lipchik RJ, Kuzo RS, Liu Y, McAuliffe TL, O'Brien DJ. Subsequent pulmonary embolism: risk after a negative helical CT pulmonary angiogram - prospective comparison with scintigraphy. *Radiology* 2000;215:535-542.
- 31 Garg K, Sieler H, Welsh CH, Johnston RJ, Russ PD. Clinical validity of helical CT being interpreted as negative for pulmonary embolism: implications for patient treatment. *AJR* 1999;172:1627-1631.
- 32 Lomis NNT, Yoon HC, Moran AG, Miller FJ. Clinical outcomes of patients after a negative spiral CT pulmonary arteriogram in the evaluation of acute pulmonary embolism. *JVIR* 1999;6:702-712.
- 33 Rathbun SW, Raskob GE, Whitsett TL. Sensitivity and specificity of helical computed tomography in the diagnosis of pulmonary embolism: a systematic review. *Ann Intern Med* 2000;132:227-232.
- 34 The COLUMBUS Investigators. Low-molecular weight heparin in the treatment of patients with venous thromboembolism. *N Engl J Med* 1997;337:657-662.
- 35 Simonneau G, Sors H, Charbonnier B, *et al.* A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. *N Engl J Med* 1997;337:663-669.
- 36 Van Erkel AR, Van Rossum AB, Bloem JL, Kievit J, Pattynama PMT. Spiral Ct angiography for suspected pulmonary embolism: a cost-effectiveness analysis. *Radiology* 1996;201:29-36.
- 37 Stein PD, Hull RD, Saltzman HA, Pineo G. Strategy for diagnosis of patients with suspected acute pulmonary embolism. *Chest* 1993;103:1553-1559.
- 38 Ginsberg JS. Management of venous thromboembolism. *N Engl J Med* 1996;335:1816-1828.
- 39 Wells PS, Ginsberg JS, Anderson DR, *et al.* Use of a clinical model for safe management of patients with suspected pulmonary embolism. *Ann Intern Med* 1998;129:997-1005.
- 40 Oudkerk M, Van Beek EJR, Van Putten WLJ, Büller HR. Cost-effectiveness analysis of various strategies in the diagnostic management of pulmonary embolism. *Arch Intern Med* 1993;153:947-954.
- 41 Van der Meer FJ, Rosendaal FR, Vandenbroucke JP, Briët E. Bleeding complications in oral anticoagulant therapy. An analysis of risk factors. *Arch Intern Med* 1993;153:1557-1562.